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(54) Title: PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

(57) Abstract

The invention relates to pharmaceutical formulations for the treatment of inflammatory bowel disease containing as active ingredient Beclomethasone dipropionate. A first aspect concerns a formulation in the form of stable and ready–to–use enema characterized in that the homogeneity of the active ingredient at low concentration (0.05 %) and fluidity of the suspension is optimal for promoting its retrograde progression and homogeneous distribution. A second aspect concerns gastro–resistant modified–release tablets whose composition has been optimized in order to control the release of the active ingredient in fluids at basic pH and low ionic strength.

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PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

The invention relates to pharmaceutical compositions for oral or rectal administration to be used for the treatment of Inflammatory Bowel Disease (IBD).

The invention more particularly relates to the use of a topically active corticosteroid, i.e. beclomethasone dipropionate, in the following also referred to as BDP, for the preparation of pharmaceutical compositions for the treatment of Inflammatory Bowel Diseases such as Ulcerative Colitis (UC) and Crohn's Disease (CD).

IBD is an inflammatory disorder of unknown cause which is characterized by a chronic relapsing - remitting course, in which relapses and remissions alternate. IBD's have increased in incidence, in particular in the Northern areas of Western Countries.

UC is characterized by an inflammatory process confined to the most superficial layer of the intestinal wall (submucosa is saved) primarily involving the colonic mucosa. One of the most frequent localizations is the rectal ampulla from which the inflammatory process can extend to the colon, but not beyond the ileo-cecal valve.

CD is yet another type of inflammatory disease of unknown etiology which mainly affects the distal ileum, but which may occur in any part of the bowel. Contrary to what is observed in UC, the inflammatory process is of "segmental" type (affected portions alternate to health areas) and it affects all intestinal layers.

The medical treatment of said diseases is based on the use of

immunosuppressive and anti-inflammatory drugs.

The most effective treatment relies on the use by oral or parenteral route of corticosteroids such as prednisolone, as they possess both immunosuppressive and antiinflammatory properties. However, their use is limited due to the possible systemic side effects (such as oedema, hypertension) and inhibitory effects on adrenocorticotropic hormone (ACTH) with consequent reduction of cortisol production by the adrenal glands. In order to avoid such consequences, the advised treatment provides for an initial high doses for a few weeks, followed by the gradual reduction to maintenance dosage, which should however still be the minimal one able of controlling the clinical symptoms.

Corticosteroids with high topical activity but low systemic bioavailability have been therefore developed; said drugs maintain an effectiveness comparable to that of the systemic ones, even though they show a reduced absorption and therefore a marked decrease in the above mentioned adverse effects

By virtue of their selective action on the affected intestinal mucosa and the high degree of first-pass metabolism in the liver, with a resulting reduction of the systemic absorption, these novel topical corticosteroids have high therapeutical effectiveness with poor incidence of both systemic and endocrine side effects.

The effectiveness of topical corticosteroids, administered in the form of enemas, in distal UC has been widely demonstrated and more recently such treatment has been also proved to be useful in patients affected by CD.

Beclomethasone dipropionate is a potent, well tolerated topical corticosteroid which has successfully been used in the treatment of distal UC.

Although being safe and effective, it has only been used in the form of galenic or extemporarily compounded preparations, as no ready-to-use formulations of suitable pharmaceutical characteristics have been commercially made available so far.

The present invention relates to ready-to-use pharmaceutical formulations for the administration of beclomethasone dipropionate (BDP) at the intestinal site, for use in the treatment of IBD.

Accordingly, a first aspect of the invention provides a physically and chemically stable enema formulation, having a small volume of administration (60 ml) and comprising 3 mg of BDP as active ingredient. Said composition is arranged so that the BDP micronized particles remain dispersed in an aqueous medium containing antimicrobials such as benzyl alcohol, methyl and propyl *p*-hydroxybenzoates, buffering salts, agents for adjusting salinity, such as sodium chloride, surfactants and/or wetting agents, such as cetostearyl alcohol, polysorbate 20 and sorbitan monolaurate and characterized by the use of xanthan gum as suspending and thickening agent.

The choice of the excipients proved to be particularly critical in order to reach the following objectives:

a) homogeneity of the active ingredient, at the low concentration of the formulation (0.05%);

b) optimised fluidity and physical stability of the suspension;

c) absence of surface interactions such as to cause crystalline growth;

d) long-term chemical stability of the active ingredient;

e) local tolerability (pH near neutrality and isotonicity);

In the treatment of Ulcerative Colitis, for an effective therapeutical action to be exerted, the active ingredient administered rectally should uniformly

spread up to the splenic flexure and further up.

Most of the BDP containing enema formulations reported until now are extemporary compounded preparations. Otherwise they envisage the use of lower doses and/or larger administration volumes.

- Levine et al (Gastroenterology 1985, 88, 1473), in a clinical study lasting 30 months, disclosed the use of formulations containing 0.5 - 4.0 mg in a volume varied from 50 to 400 ml to be administered daily or b.i.d.
- Mulder et al (Eur. J. Gastroenterol & Hepatol 8, 549-553, 1996), in a study aiming at comparing the efficacy of BDP vs. 5-ASA, employed enemas containing 3 mg in 100 ml.
- US 4350690 claims enema formulations containing between 0.1 to 2.0 mg in a volume from about 50 to 150 ml. Said formulations have been extemporary prepared and no stability data are reported.
- Kumana et al (Clin. Chem. 1981, 27, 1049; Lancet 1982, 1(8272), 579) employed enema formulations at low dose (1 mg) in order to avoid any systemic effects According to the authors, said formulations are stable but it is not reported for how long.

US 5, 378,470 claims pharmaceutical compositions for rectal use as dry material to be reconstituted immediately before use.

Bansky et al. (Dis Colon & Rectum 1987, 30(4), 288-292), for the same reason (i.e. to avoid systemic effects) utilise formulations containing 0.5 mg in 100 ml. Said formulations, comprising polysorbate 80, methyl p-hydroxy benzoate, sodium edetate and citric acid to pH 4.25, turned out to be stable for 12 months.

Vignotti et al. (Cur. Ther. Res. 52, 659 - 665, 1992) and D'Arienzo et al. (It. J. Gastroenterol & Hepatol 30, 254-257, 1998) reported on clinical efficacy

of 60 ml enema containing 3 mg of BDP, but the characteristics of the formulation are not disclosed.

The enema formulation of the invention has optimized characteristics of viscosity in order to promote its retrograde progression and homogeneous distribution of the active ingredient on all the interested area; the effective therapeutical action is exerted locally, without inducing any significant side effects by keeping low the concentration of the active ingredient, in a small administration volume (3 mg in 60 ml).

It has been indeed found that xanthan gum is particularly effective in providing said optimized characteristics of viscosity, so that the active ingredient, upon rectal administration of the formulation, is able to reach, by retrograde progression, the sigmoid colon and the descending colon until to the splenic flexure and further up to the intestinal mucosa affected by the pathological process. In the known art, enema are generally not able to pass beyond the left side of the colon.

The pH and the salinity of the formulation of the invention have been also adjusted to physiological values, i.e. pH approximately 7 and osmolarity of about 280 Mosm/l, to make it well tolerated and to avoid further possible irritating effects against the inflamed mucosa.

Furthermore, the formulation of the invention turned out to be physically and chemically stable for at least three years, as it can be appreciated from the evaluation of the most significant chemical and technological parameters upon long-term storage conditions. This makes its use and the commercial distribution considerably easier.

The stability of the formulation of the invention at a pH of about 7 is an unexpected result. In the prior art (Foe et al. Biopharm. Drug Dispos. 19, 1-8,

1998), it is reported indeed that dissolved BDP in 0.002-0.004% phosphate buffer suspension at pH 7.4 undergoes a slow but considerable degradation due to hydrolysis. Said reaction could result, upon long-term periods as those envisaged for storing pharmaceutical formulations, in a decrease of the content which do not conform with the ICH (International Conference Harmonisation) requirements.

Finally, the formulation of the invention turned out to be stable without adding stabilizers such as anti-oxidants. It is well known indeed that some of the agents commonly utilised for this purpose may give rise to irritation or allergic reactions.

According to a second aspect, the invention provides a formulation for distal ileum and proximal colon delivery in the form of modified-release tablets formed by a central core which allows sustained release of the active ingredient (BDP) coated with a polymeric gastroresistant coating.

In order to meet the pharmacological need for a local antiinflammatory action, a tablet for the treatment of inflammatory bowel disease should be able of delivering the active ingredient as near as possible to the action site.

The ideal approach is the specific delivery of the active ingredient to the colon. The formulations for colonic delivery should be designed to withstand both low and slightly basic pH values for several hours. During this time they are assumed to pass the stomach and the small intestine and to reach the large intestine where the coat disintegrates and the drug release process is initiated. The polymers used for this purpose are commonly acrylic acid derivatives or cellulose derivatives. More difficult to predict is the location, and hence the environment, in which the coat starts to degrade. Depending on the gastrointestinal mobility pattern, it can occur deep in the colon, as well as

halfway down the small intestine. In addition, the presence of short-chain fatty acids, carbon dioxide, and other fermentation products, often reduces the pH of the ascending colon and call in question the use of the pH just to trigger drug release. Therefore the problem cannot be solved by using only a particular gastro-resistant polymeric coating as, in many cases, a significant amount of the active ingredient could be released prior to the arrival at the targeted site.

In the prior art different approaches are reported in order to target as much drug as possible to the desired location (i.e colon) where it should exert its therapeutic activity.

WO 9116881, WO 9200732 e WO 97/27843 all claim different kind of pharmaceutical compositions characterised in that the coating and/or the matrix is a substance e.g a polysaccharide such as pectin or its derivatives which is specifically attacked by intestinal bacteria.

EP 0521074 claims a special osmotic device whose enteric coat is hydrophobic for preventing the flux of water through said coating. The corresponding formulations are of complicated design and manufacture.

Furthermore, it is well known that the ionic strength of the medium could affect the properties of some of the hydrophobic excipients used at this purpose and, hence, the disintegration rate of the tablets. The gastric-intestinal fluids of the patients at which said formulations are addressed to, are expected to be poor in salts and, hence, of low ionic strength; accordingly the choice of the excipients and the corresponding ratios should be evaluated in view of such potential drawbacks.

A simple solution is provided by the modified-release tablet of the invention which has the following characterizing features:

1) a gastro-resistant coating, made of a film of methacrylic acid copolymer in

aqueous phase;

2) a sustained-release core, obtained by using hydroxypropylmethyl cellulose, in concentration ranging from 15 to 35% by weight on the core weight;

3) a ratio between water soluble and insoluble excipients of approximately 5:3 *w/w* where the amount of soluble excipients does not exceed 60% by weight of the weight of the tablet.

It has been surprisingly found that the choice of the excipients and in particular the ratio between the water soluble and insoluble excipients is of paramount importance for controlling the disintegration of the tablets and, hence, for triggering the release of the drug in fluids of low ionic strength. The compositions of the inventions are stable, simple to make and allow most of the dose to be released at the targeted site (distal ileum and proximal colon).

Other hydrophobic excipients for controlling the release of the drug such as hydroxypropyl cellulose and methyl cellulose and other polymers resistant up to pH 5.5, such as cellulose phthalate derivatives, for coating the tablets can be advantageously used.

The preparation of the formulations is illustrated in greater detail in the following examples which are not meant to be limiting the invention.

Example 1. Preparation of 1000 bottles of BDP enemas

Ingredients:

Beclomethasone dipropionate	30 g
Polysorbate 20	600 g
Sorbitan monolaurate	120 g
Methyl parahydroxy benzoate	1080 g
Propyl parahydroxy benzoate	180 g
Benzyl alcohol	3000 g

Xanthan gum	3000 g
Cetostearyl alcohol	780 g
Monobasic potassium phosphate	2124 g
Dibasic sodium phosphate dihydrate	4344 g
Sodium chloride	2520 g
Purified water q.s. to	600 l

Methyl *p*-hydroxy benzoate and propyl *p*-hydroxy benzoate are added to water heated to 83÷88°C, and solubilised with the aid of a turbine. The solution is cooled down to 70÷75°C, cetostearyl alcohol, polysorbate 20 and sorbitan monolaurate, benzyl alcohol, potassium phosphate salts, sodium phosphate and sodium chloride are added, and the resulting suspension is stirred. The preparation is cooled down to 42÷45°C, than the active ingredient is added under stirring.. The xanthan gum is dispersed, under stirring. The final volume is controlled, adding water if necessary. The suspension is stirred under vacuum and cooled down to room temperature. The pH is approximately 7.0

Example 2. Preparation of BDP modified-release tablets

Unitary composition

Ingredients:

Micronized beclomethasone dipropionate	5.0 mg
Spray dried lactose F.U.	48.4 mg
Microcrystalline cellulose (Avicel®PH 102)	8.0 mg
Maize starch	3.0 mg
Hydroxypropyl methyl cellulose 2208 (Methocel® K4M)	20.0 mg
Magnesium stearate	0.6 mg
	85.0 mg

Gastro-resistant coating:

Film made of methacrylic acid copolymer (Eudragit ® L 30 D).

First, the core is prepared as follows. BDP is dispersed in half the amount of spray dried lactose. All the components are sieved through a 25 mesh sieve, the BDP/lactose premix is mixed with the other components and compressed. Finally, cores are coated.

Example 3. Evaluation of the retrograde progression of the enemas.

In order to assess the capability of the medicament to reach the inflammation site, a test was performed using a scintigraphic technique well known in literature, which is suitable to detect the extension and limits of the retrograde progression of BDP enemas.

BDP rectal enema was radiolabeled with technetium 99 m ($^{99}Tc^{m}$) colloidal sulfide and administered in single 3 mg dose to 8 adult patients with distal ulcerative colitis moderately active or in remission. Scintigraphic recordings were then carried out at 5, 30, 60, 120, 180, 210 and 240 minutes after dosing, with patients lying face upwards. Total radioactivity (COU), pixel number (CELL) and mean radioactivity per pixel (AVG) in the different intestinal portions were evaluated.

The resulting data showed a significant difference of the "retrograde spread" of BDP enemas in patients with active distal ulcerative colitis and in remission patients. Whereas in the latter the upward progression of the radiolabelled solution stopped at the first tracts of the intestine, in the patients with active ulcerative colitis the retroprogression of BDP enemas was much more extended, reaching, in some cases, the hepatic flexure, thus meeting the expected requirements.

Example 4. Disintegration and release characteristics of the tablets

Disintegration.

Disintegration parameters were evaluated according to the Official Pharmacopoeia (F.U.).

According to F.U., gastric resistant tablets should show no signs of disgregation or fracture upon immersion at pH 1.2 for 2 hours, and should disintegrate within a time of 60' at most, at pH 6.8.

The disintegration rate of the tablets of the invention was also checked in buffer solutions with different ionic strengths.

In particular, the solutions at different pH and ionic strength reported as follows were used:

Solutions and relevant pH		Ionic strength (I)
1	Phosphate buffer solution F.U. pH 6.8	0.6
2	Phosphate buffer solution F.U. pH 6.8	0.4
3	Phosphate buffer solution IDMA pH 6.9	0.1
4	Phosphate buffer solution pH 6.8	0.1
5	0.1 N HCl solution	0.1
6	0.1 N HCl solution + 0.9% NaCl	0.2
7	0.1 N HCl solution + 9% NaCl	1.6

The corresponding disintegration time of the sustained-release core of the tablets of the invention, are reported as follows:

Solution	Time (min)
Solution 1	5
Solution 2	5
Solution 3	60
Solution 4	150
Solution 5	150
Solution 6	>60
Solution 7	6

A similar behavior was observed for the tablets with gastro-resistant coating when tested at pH 6.8 - 6.9.

As it can be inferred from the obtained results, the tablets are significantly affected by the different ionic strengths. Said test is of paramount importance in order to predict the *in vivo* disintegration time of the tablets, as the formulation is addressed to patients whose salt concentration in the intestinal fluids is probably reduced.

F.U. advises indeed a medium for carrying out the test whose salt concentration is much higher than that present in the body; therefore the *in vivo* disintegration behavior of the tablets of the invention is more likely to correspond to that observed in buffers 3 and 4; in said buffers, the ionic strength is lower as it has been adjusted for better simulate the conditions of the intestinal fluids of a patient affected by IBD..

The disintegration behavior of the tablets was also evaluated *in vivo*, at the intestinal site, in a study carried out on 8 healthy volunteers. A scintigraphic technique was employed as it is suitable for evaluating the position and integrity of the tablet within the gastrointestinal tract (Steed K.P. et al. Int J

Pharmaceutics 1994; 112:199-206). The results confirmed that the tablet does not disintegrate in the stomach: the scintigraphic images evidence that onset of the erosion occurs in the small intestine and in the proximal colon, gradually continuing in the intestinal transit, so that most of the dose can reach the distal intestine. These findings confirmed that the modified-relase tablets of the invention meet the requirements considered necessary for a formulation designed for the topical treatment of inflammatory bowel disease.

Release

In order to evaluate the release characteristics of the active ingredient from the tablets, a test was carried out using the apparatus for the determination of the disintegration time of tablets, reported in F.U. IX edition, vol. I, page 403, according to the conditions reported in USPXX/NFXV page 959 (apparatus n. 3 for the dissolution test).

The tablets were immersed in media with pH varying in progression from 1.5 to 7.2. The test was carried out for eight hours.

As the active ingredient is insoluble in water, it was considered 'dissolved' once it was present as dispersed particles into the medium. Said particles were subsequently dissolved in ethanol for the spectrophotometric determination. To avoid interferences, the analyses were carried out with comparison to a blank. Solutions with increasing pH: 1.5 - 4.5 - 6.9 - 7.2, in a 900 ml volume, were used. Four tablets were placed in the basket of the apparatus and 900 ml of the medium at pH 1.5 pre-heated to 37°C±0.5°C, were added; the vessel was kept under stirring for one hour. The test liquid was discarded and replaced with 900 ml of the medium at pH = 4.5, operating under the same conditions. The test was then continued with the medium at pH = 6.9, keeping the vessel under stirring for two hours and finally with the medium at

pH = 7.2, under stirring for four hours. Samples (10 ml) were withdrawn after 1, 2,4,6 and 8 hours.

The results are reported as follows:

Sample	pH	Partial time	Total time	% release
1	1.5	1 hour	1 hour	0
2	4.5	1 hour	2 hours	0.9
3	6.9	2 hours	4 hours	36.0
4	7.2	2 hours	6 hours	32.4
5	7.2	2 hours	8 hours	31.2
				100.5

Example 5. Evaluation of the absorption.

In order to demonstrate that no systemic absorption occurred, BDP and its major active metabolites, Beclomethasone-17-monopropionate (B17MP) and Beclomethasone (BOH), were determined in plasma and urine samples in subjects undergoing treatment with the formulations of the invention.

A first study was performed in 9 healthy male volunteers, after a single administration of enemas by rectal route and a single administration of a gastro-resistant modified-release tablet by oral route. No detectable amounts of the drug and its metabolites were found on plasma and urine samples, indicating that, upon both the rectal and the oral administrations, the BDP activity is exerted only topically.

A subsequent study carried out in 10 ileostomized patients, 5 of whom treated with 5 mg modified-release BDP coated tablets and the other 5 with 5 mg BDP uncoated tablets, confirmed the absence of the active ingredient and of

its metabolites both in plasma and urine samples collected during the study. The analysis of intestinal effluates showed the presence of significant amounts of BDP and B17MP, indicating that a significant release of active ingredient occurred at the action site, i.e. the distal part of the ileum. A higher release was observed for the gastro-resistant formulation

The absence of systemic absorption of unmetabolised BDP and/or of its metabolites was also assessed in a pharmacokinetic-scintigraphic study performed in healthy volunteers (example 4, § "Disintegration"), to further confirm the topical action of the compound.

Example 6. Stability of enemas BDP formulation

The long-term stability (21-24° C, 52-60% R.H.) was evaluated after storing the formulation in polyethylene flasks. The results are reported in Table 1. The BDP content was determined by HPLC. The other following parameters were monitored: appearance, pH, viscosity and the microbial count according to Ph. Eur. III Ed.

In said conditions, the formulation turned out to be stable for at least three years.

Table 1

Parameter	Appearance	pH	Viscosity (cp)	BDP Content (%)	Microbial count
Time : 0	Homogeneous	6.97	800	100	complies
: 6 months	unchanged	6.96	810	104.0	n.d.
: 12 months	unchanged	6.95	860	103.3	n.d.
: 18 months	unchanged	6.95	815	98.5	n.d.
: 24 months	unchanged	6.56	800	98.5	n.d.
: 36 months	unchanged	6.48	795	100.4	complies

n.d. not determined

CLAIMS

1. Pharmaceutical formulation for the treatment of inflammatory bowel disease, in the form of stable, ready-to-use enema, said formulation:
consisting of 3 mg of beclomethasone dipropionate as active ingredient suspended in 60 ml of an isotonic aqueous medium ;
having pH between 6.5 and 7.5;
containing xanthan gum as suspending and thickening agent.

2. Pharmaceutical formulation according to claim 1, further comprising antimicrobials, buffering salts and surfactants and/or wetting agents.

3. Pharmaceutical formulation according to claim 2, wherein the antimicrobials are benzyl alcohol, methyl and propyl p-hydroxybenzoates, and the surfactants and/or wetting agents are cetostearyl alcohol, polysorbate 20 and sorbitan monolaurate.

4. A pharmaceutical formulation for the treatment of inflammatory bowel disease in the form of a gastro-resistant modified-release tablet formed by an outer polymeric coating resistant up to pH 5.5 and a central core characterized in that it contains: i) beclomethasone dipropionate as active ingredient ii) an hydrophobic excipient for controlling the release of the active ingredient in concentrations ranging from 15 to 35% by weight on the core weight; iii) a ratio between water soluble and insoluble excipients of approximately 5:3 w/w where the amount of soluble excipients does not exceed 60% by weight on the weight of the tablet.

5. Pharmaceutical formulation according to claim 4, wherein the active ingredient is beclomethasone dipropionate.

6. Pharmaceutical formulation according to claim 4, wherein the enteric

coating is made of methacrylic acid or cellulose phthalate polymers, preferably Eudragit®L 30 D.

7. Pharmaceutical formulation according to claim 4, wherein the hydrophobic excipient is a hydroxypropylmethyl cellulose, hydroxypropyl cellulose or methyl cellulose, preferably Methocel® K4M, to provide the gradual and controlled release of the active ingredient in fluids at basic pH and low ionic strength.